S/N Unknown **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	David J. Grainger et al.	Examiner: Unknown
Serial No.:	Unknown	Group Art Unit: Unknown
Filed:	Herewith	Docket: 295.009US3
Title:	PREVENTION AND TREATMENT OF CARDIOVASCULAR PATHOLOGIES	

PRELIMINARY AMENDMENT

BOX PATENT APPLICATION
Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend the above-identified application as follows:

IN THE SPECIFICATION

At page 1, line 1, please insert the following:

-- **Cross-Reference to Related Applications**

This application is a continuation application of U.S. application Serial No. 08/973,570, filed December 5, 1997, which is a national stage filing of PCT/US96/10211, filed June 7, 1996, which is a continuation-in-part of U.S. application Serial No. 08/478,936, filed June 7, 1995, abandoned; U.S. application 08/476,735, filed June 7, 1995, now U.S. Patent No. 5,595,722; U.S. application Serial No. 08/477,393, filed June 7, 1995, pending; and U.S. application Serial No. 08/486,334, filed June 7, 1995, now U.S. Patent No. 5,770,609. -- .

Please enter the amended sheets for pages, 110-134 (which amended claims 22-152) and page 135 which contains the Abstract, that are attached to the International Preliminary Examination Report dated August 26, 1997.

IN THE CLAIMS

Please cancel claims 1-62, 64, 66, 90-94, and 117 without prejudice.

Please amend the claims as follows:

67. (Amended) The method of claim [61, 62 or] 63 wherein the compound of formula (I) is idoxifene or a pharmaceutically acceptable salt thereof.

68. (Amended) The method of claim [21, 61, 62 or] 63 wherein the compound of formula (I) is toremifene or a pharmaceutically acceptable salt thereof.

69. (Amended) The method of claim [61, 62 or] 63 wherein the administration is to a human patient.

70. (Amended) The method of claim [61, 62 or] 63 wherein the administration is before, during or after said procedure.

71. (Amended) The method of claim [61, 62 or] 63 wherein the administration is in a series of spaced doses.

72. (Amended) The method of claim [61, 62 or] 63 wherein the administration is parenteral.

73. (Amended) The method of claim [61, 62 or] 63 wherein the administration is oral.

74. (Amended) The method of claim [61, 62 or] 63 wherein the administration is systemic.

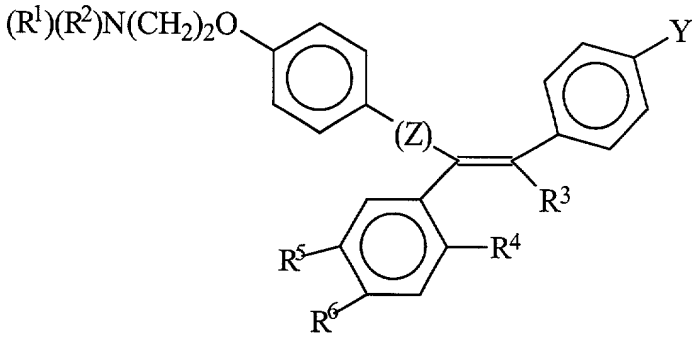
75. (Amended) The method of claim [61, 62 or] 63 wherein the compound of formula (I) is administered via a sustained release dosage form.

76. (Amended) The method of claim [61, 62 or] 63 wherein the administration is localized at the site of the vascular trauma.

77. (Amended) The method of claim [61, 62 or] 63 wherein the compound directly or indirectly increases the level of active TGF-beta.

80. (Amended) A therapeutic method for preventing or treating a cardiovascular or vascular indication characterized by a decreased lumen diameter comprising administering to a mammal at risk of or afflicted with said cardiovascular or vascular indication, a cytostatic

dose of a therapeutic agent, wherein the therapeutic agent is a compound of formula (I):



(I)

wherein Z is C=O or a covalent bond; Y is H or $O(C_1-C_4)$alkyl, R^1 and R^2 are individually (C_1-C_4)alkyl or together with N are a saturated heterocyclic group, R^3 is ethyl or chloroethyl, R^4 is H, R^5 is I, $O(C_1-C_4)$alkyl or H and R^6 is I, $O(C_1-C_4)$alkyl or H with the proviso that when R^4, R^5, and R^6 are H, R^3 is not ethyl; or a pharmaceutically acceptable salt thereof.

81. (Amended) The method of claim 80 wherein the cytostatic dose is effective to increase the level of TGF-beta so as to [decrease lesion formation or development,] <u>inhibit smooth muscle cell proliferation,</u> inhibit lipid accumulation, increase plaque stability, maintain or increase vessel lumen diameter, or any combination thereof.

95. (Amended) The method of claim 89 [or 90] wherein the increase in TGF-beta reduces or inhibits diabetic retinopathy.

99. (Amended) The method of claim [1, 2, 21 or] 89 wherein the compound is a TGF-beta production stimulator.

100. (Amended) The method of claim [1, 2, 21 or] 89 wherein the compound is a TGF-beta activator.

101. (Amended) The method of claim [1, 2, 21 or] 89 wherein the compound increases the production of TGF-beta mRNA.

102. (Amended) The method of claim [1, 2, 21 or] 89 wherein the compound increases the cleavage of the latent form of TGF-beta.

103. (Amended) The method of claim [1, 2, 21 or] 89 wherein the compound increases the bioavailability of TGF-beta.

108. (Amended) The method of claim [1, 2, 21, 61, 62,] 63 [, 80 or] 89 wherein the compound forms cellular DNA adducts at level which is reduced relative to DNA adduct formation by tamoxifen.

109. (Amended) The method of claim [1, 2, 21, 61, 62,] 63 [, 80 or] 89 wherein the compound has estrogenic activity which is reduced relative to the estrogenic activity of tamoxifen.

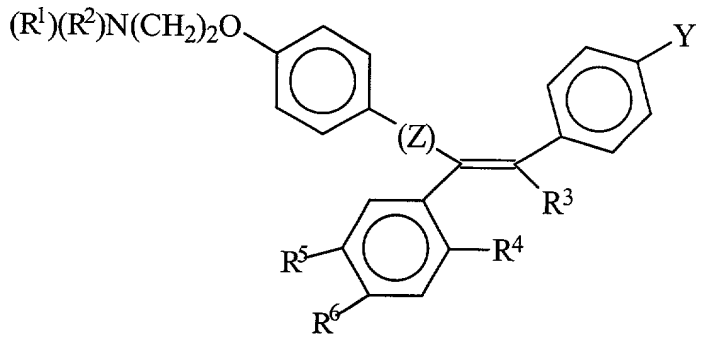
110. (Amended) The method of claim [21, 61, 62, 63 [, 80 or] 89 wherein the compound does not form cellular DNA adducts.

111. (Amended) The method of claim [1, 2, 21, 61, 62, 63 [, 80 or] 89 wherein the compound has no estrogenic activity.

118. (Amended) The method of claim [1, 2, 21, 61, 62,] 63, [80,] 89[, 90] or 112 wherein the administration increases the level of latent TGF-beta relative to the level of latent TGF-beta prior to said administration.

119. (Amended) The method of claim [1, 2, 21, 61, 62,] 63, [80,] 89[, 90] or 112 wherein the administration increases the level of active TGF-beta relative to the level of active TGF-beta prior to said administration.

120. (Amended) A therapeutic method for preventing or treating a [cardiovascular or] vascular indication characterized by a decreased lumen diameter comprising administering to a mammal at risk of or afflicted with said [cardiovascular or] vascular indication, a cytostatic dose of a therapeutic agent, wherein the therapeutic agent is a compound of formula (I):



(I)

wherein Z is C=O or a covalent bond; Y is H or O(C_1-C_4)alkyl, R^1 and R^2 are individually (C_1-C_4)alkyl or together with N are a saturated heterocyclic group, R^3 is ethyl or chloroethyl, R^4 is H or together with R^3 is -CH_2-CH_2- or -S-, R^5 is I, OH, O(C_1-C_4)alkyl or H and R^6 is I, O(C_1-C_4)alkyl or H with the proviso that when R^4, R^5 and R^6 are H, R^3 is not ethyl; or a pharmaceutically acceptable salt thereof.

135. (Amended) The intravascular stent of [any one of claims 122 to 129] claim 129 wherein the compound of formula (I) is in a sustained release dosage form.

136. (Amended) The intravascular stent of [any one of claims 122 to 129] claim 129 wherein the matrix of the stent comprises the compound of formula (I).

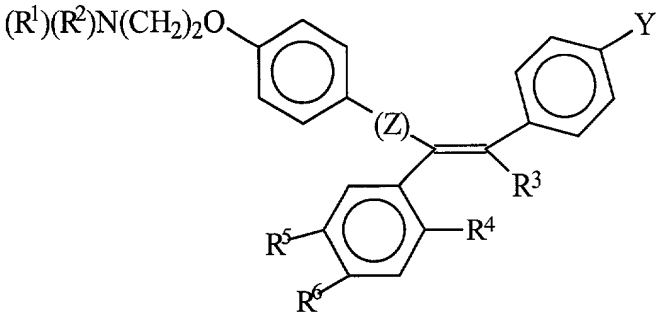
Please add the following new claims:

153. (New) The method of claim 120 wherein the compound of formula (I) is idoxifene, 4-iodotamoxifen, 3-iodotamoxifen, toremifene, or a pharmaceutically acceptable salt thereof.

154. (New) The method of claim 120 wherein the administration is systemic.

155. (New) The method of claim 120 wherein the compound of formula (I) is administered in a sustained release dosage form.

156. (New) A therapeutic method for treating a condition selected from the group consisting of arteriosclerosis and small vessel disease, comprising administering to a mammal afflicted with said condition, an effective amount of a compound of formula (I):

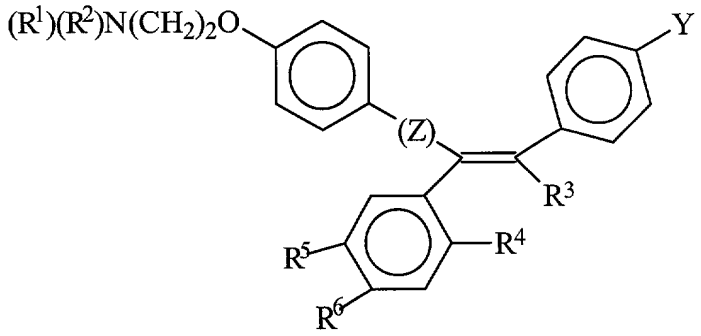


(I)

wherein Z is C=O or a covalent bond; Y is H or O(C_1-C_4)alkyl, R^1 and R^2 are individually (C_1-C_4)alkyl or together with N are a saturated heterocyclic group, R^3 is ethyl or

chloroethyl, R^4 is H, R^5 is I, $O(C_1\text{-}C_4)$alkyl or H and R^6 is I, $O(C_1\text{-}C_4)$alkyl or H with the proviso that when R^4, R^5, and R^6 are H, R^3 is not ethyl; or a pharmaceutically acceptable salt thereof.

157. (New) A method of treating diabetic retinopathy by increasing the level of TGF-beta in a mammal in need thereof, comprising administering an effective amount of a compound of formula (I):



(I)

wherein Z is C=O or a covalent bond; Y is H or $O(C_1\text{-}C_4)$alkyl, R^1 and R^2 are individually $(C_1\text{-}C_4)$alkyl or together with N are a saturated heterocyclic group, R^3 is ethyl or chloroethyl, R^4 is H or together with R^3 is $-CH_2\text{-}CH_2-$ or -S-, R^5 is I, OH, $O(C_1\text{-}C_4)$alkyl or H and R^6 is I, $O(C_1\text{-}C_4)$alkyl or H with the proviso that when R^4, R^5, and R^6 are H, R^3 is not ethyl; or a pharmaceutically acceptable salt thereof.

REMARKS

Applicant respectfully requests that the Preliminary Amendment described herein be entered into the record prior to examination of the above-identified application.

Claims 67–77, 95, 99-103, 108-111, and 118-119 are amended to recite proper antecedent basis.

Support for the amendment to claim 80 is provided in the specification at page 3, lines 8-6; page 5, lines 12-17; page 10, line 10-page 11, lines 1; page 12, lines 11-14; and in claim 80 as

originally filed.

Support for the amendment to claim 81 is found in the specification at page 3, lines 18-20 and claim 81 as originally filed.

Support for the amendment to claim 120 is found in the specification at page 3, lines 5-16; and claim 120 as originally filed.

Support for newly added claim 153 is found in the specification at page 3, line 20-page 4, line 4; and page 9, lines 10-18.

Support for newly added claim 154 is found in the specification at page 4, lines 5-7; and page 5, lines 12-20.

Support for newly added claim 155 is found in the specification at page 5, lines 17-20; page 16, lines 10-13; and page 28-lines 10-12.

Support for newly added claim 156 is found in the specification at page 10, lines 29-31 and page 12, lines 11-14.

Support for newly added claim 157 is found in the specification at page 12, lines 12-14; page 17, lines 4-20; and in originally filed claims 95 and 97.

Respectfully submitted,

DAVID J. GRAINGER ET AL.,

By their Representatives,

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 373-6959

Date January 4, 2001 By _____
Janet E. Embretson
Reg. No. 39,665

"Express Mail" mailing label number: EL618437376US
Date of Deposit: January 4, 2001
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